

Remarks/Arguments

The specification has been amended to comply with the formal requirements of using trademarks in a patent application.

Prior to the present amendment, claims 1-49 were pending in this application. Claims 1-13 and 29-49 have been withdrawn from consideration, and claims 14-29 have been rejected. The present amendment includes the cancellation of claim 17, and of non-elected claims 1-13 and 29-49, and the amendment of claims 14, 16, 18-20, and 22-26. All amendments are fully supported by the specification, and do not add new matter. The amendments were made without prejudice or disclaimer. Applicants specifically reserve the right to pursue any deleted subject matter in one or more continuing applications.

Election/Restrictions

Applicants were requested to elect, for examination purposes one of the following groups:

- I. Claims 1-13, drawn to a method for inhibiting interleukin-17 (IL-17) production by T cells;
- II. Claims 14-28, drawn to a method for the treatment of an inflammatory disease;
- III. Claims 29-37, drawn to a method for identifying an anti-inflammatory agent;
- IV. Claims 38-47, drawn to a method for inducing IL-17 production in a mammalian subject.

The oral election of the invention of Group II, claims 14-28 is hereby affirmed.

Priority

Applicants note that the October 30, 2002 filing date of provisional application 60/423,090 has been acknowledged as the earliest effective filing date of the instant application.

Information Disclosure Statement

Applicants note and appreciate consideration of the Information Disclosure Statements received on January 18, 2005 and January 25, 2006, respectively.

Specification

The specification has been objected to for its incorrect use of certain trademarks. The foregoing amendment to the specification, which includes capitalization of the trademarks in question, and addition of applicable general terminology whenever available, is believed to obviate this objection.

Claims Rejections – 35 U.S.C. § 112, first paragraph - enablement

(1) Claims 14-28 have been rejected under 35 U.S.C. 112, first paragraph for allegedly failing to comply with the enablement requirement. According to the rejection, “the specification, while being enabling for treating diseases characterized by delayed-type hypersensitivity, as described in Example 2, does not reasonably provide enablement for any other treatment of any other disease characterized by elevated expression of IL-17.” The Examiner acknowledges that “the specification, on pages 1-2 and 22-23 recites diseases that are characterized by elevated IL-17 expression, the specification provides no guidance or working examples that teach that these, or any other disease, can be treated by administration of an IL-12 antagonist.” The Examiner adds that (1) the “specification only shows an example showing that IL-23p19-deficient mice exhibit decreased delayed-type hypersensitivity reactions,” (2) decreasing IL-23 by genetic knock-out of the IL-23p19 gene in mice “may not necessarily reflect pathological conditions in a genetically intact animals with inflammatory disease, and (3) “the data presented in Example 2 was not generated by administration of any IL-23 antagonist.” From this, the Examiner concludes that undue experimentation would be needed to practice the invention within the full scope of the rejected claims.

Applicants disagree, and respectfully traverse the rejection.

The rejection disregards the core finding underlying the present invention: the recognition that there is a correlation between the expression and biological roles of two otherwise known cytokines, IL-17 and IL-23.

In Example 1 (Figures 2, 3) Applicants have demonstrated experimentally that IL-23 stimulates the production of IL-17 in cell culture. In the same Example, Applicants have shown

that IL-23-mediated IL-17 production was completely blocked in the presence of a neutralizing antibody that interacts with the p40 subunit of IL-12 (Figure 4A, left panel). This antibody also inhibited more than 50 % the induction of IL-17 production observed in response to conditioned media from LPS stimulated dendritic cells (Figure 4A, right panel). Since the p40 subunit is shared between IL-12 and IL-23, the antibody used in this experiment was an IL-23 antagonist, and the results demonstrate that an IL-23 antagonist (an anti-IL-23 antibody) is capable of inhibiting IL-17 production.

As discussed in the Description of Related Art section of the specification and in paragraphs [0067] – [0074], at the effective filing date of the present application IL-17 was known to be a pro-inflammatory cytokine that is produced by activated T cells, and was implicated in a variety of inflammatory diseases, including rheumatoid arthritis (RA), Behcet's disease, asthma, systemic lupus erythematosus, psoriasis, and multiple sclerosis. Accordingly, from the ability of an IL-23 antagonist to block IL-17 production, as demonstrated in Example 1, one of ordinary skill in the art at the effective filing date of the present application would have reasonably concluded that IL-23 antagonists, such as IL-23 antibodies, could be used to treat diseases characterized by an elevated expression of IL-17 with a reasonable expectation of success. The *in vivo* results set forth in Example 2 further strengthen this conclusion, in that they establish that the role of IL-23 is distinct from the role of IL-12, with which it shares a subunit and further that IL-23p19 deficient mice phenotypically resemble IL-17 mice.

Since, as discussed above, IL-17 was known to be involved in various inflammatory diseases at the effective filing date of the present application, based on Applicants' demonstration of the correlation between the biological roles of IL-17 and IL-23, and the overall teaching provided in the specification of the present application, one of ordinary skill in the art was able to use IL-23 antagonists for the treatment of inflammatory diseases characterized by elevated expression of IL-17, without undue experimentation.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(2) Claims 14-28 have been rejected under 35 .S.C. 112, first paragraph as allegedly failing to comply with the enablement requirement. According to the rejection, while the

specification is “enabling for IL-23 antagonists that are anti-IL-23 antibodies or anti-IL23 receptor antibodies, [it] does not reasonably provide enablement for any other IL-23 antagonists.”

Without acquiescing to the rejection, and solely to advance prosecution, the rejected claims now recite anti-IL-23 antibodies and anti-IL23 receptor antibodies, for which the specification has been found to be enabling. Accordingly, the present rejection should be withdrawn.

(3) Claims 20 and 21 were rejected under 35 U.S.C. 112, first paragraph, “because the specification, while being enabling for Fv, Fab, Fab’, or Fa(ab’)₂ antibody fragments, does not reasonably provide enablement for any other antibody fragment.” According to the rejection, the specification does not teach any antibody fragments apart from those listed above, does not have any guidance or working examples at all of any antibody fragment that could act as an IL-23 antagonist. Therefore, a “person of ordinary skill in the art . . . would not be able to predict which of the many possible fragments of an anti-IL-23 antibody could act as antagonists of IL-23.”

Applicants strongly disagree, and traverse this rejection.

Proper assessment of compliance with the enablement requirement of 35 U.S.C. 112, first paragraph requires a legal analysis under In re Wands, 858 F.2d 731 (Fed. Cir.1988), in order to determine whether the scope of the claims bears a reasonable correlation to the scope of enablement provided in the specification to persons of ordinary skill in the art. In re Fisher, 427 F.2d 833 (CCPA 1970). Such legal analysis is not advanced in support of the present rejection, and therefore, a *prima facie* case of non-enablement has not been established.

In addition to Fv, Fab, Fab’, or Fa(ab’)₂ fragments, the definition of antibody fragments provided in paragraph [0029] of the specification lists, by way of example, diabodies, linear antibodies, single-chain antibody molecules, and multispecific antibodies formed from antibody fragments. Methods for making antibodies, including antibody fragments, were well known in the art at the earliest effective filing date of the present application, and are also discussed between paragraph [0051] and paragraph [0065] of the specification. This discussion includes

detailed teaching about the phage display technology, which is commonly used for the production of libraries of antibody fragments. In addition, in paragraphs [0064] and [0065] the specification provides specific teaching for the production of antibody fragments including heteroconjugate antibodies. This teaching, coupled with general knowledge in the art at the effective filing date of the present application, as represented, for example, by the text books referenced in paragraph [0066], leaves no doubt that at the relevant time a person of ordinary skill was able to prepare antibody fragments in general, not limited to Fv, Fab, Fab', or Fa(ab')₂ fragments, without undue experimentation.

It is submitted that, based on the disclosure provided in the specification and general knowledge in the art, the same person of ordinary skill was also able to use such antibody fragments as IL-23 antagonists, without undue experimentation. Screening assays to identify IL-23 antagonists are described in paragraphs [0040] – [0049] of the specification. There is no reason why antibody fragments that act as IL-23 antibodies could not be identified by using such assays.

Indeed, by acknowledging enablement for Fv, Fab, Fab', or Fa(ab')₂ fragments, the Examiner has inherently accepted that the production and use of such antibody fragments was enabled, but gave no reason why the production or use of other antibody fragments would pose difficulties that could only be overcome by undue experimentation. Applicants submit that such undue experimentation is not required, and respectfully request the reconsideration and withdrawal of the present rejection.

Claim Rejections – 35 USC § 112, first paragraph – written description

Claims 14-28 were rejected under 35 U.S.C. 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The rejection is based on the alleged lack of adequate written description for IL-23 antagonists other than anti-IL-23 antibodies or anti-IL-23 receptor antibodies.

Without acquiescence to the rejection, and solely to expedite prosecution, the claims now recite methods using anti-IL-23 antibodies or anti-IL-23 receptor antibodies, which is believed to obviate the present rejection.

Claim Rejections – 35 USC § 102

Claims 14-28 have been rejected under 35 U.S.C. 102(e) as allegedly being anticipated by Chirica et al. (US 6,756,481). Chirica et al. is cited for its teaching of the IL-23 receptor subunit, antibodies and antibody fragments specifically binding to such subunit, and that IL-23 receptor antagonists can be used to treat multiple sclerosis, psoriasis, and rheumatoid arthritis, “all of which are disclosed in the instant application as disorders associated with increased IL-17 expression.”

The rejection is respectfully traversed.

Claim 14, as currently amended, recites that the IL-23 antibody or IL-23 receptor antibody is administered to a mammalian subject determined to express an elevated level of IL-17. Chirica et al. does not teach the relationship between IL-17 expression and IL-23, and the determination of elevated IL-17 levels in the patient as a precondition to treatment with IL-23 receptor antibodies. Accordingly, Chirica et al. does not anticipate claim 14, nor the other claims, which all depend from claim 14, carrying its recitations, and the present rejection should be withdrawn.

Drawing Corrections

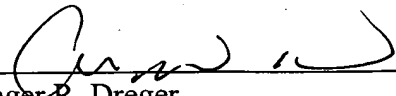
In order to address the issues raised in the Notice of Draft Persons’ Patent Drawing Review, enclosed are new Figures 6A-6C; 8A – 8F; 10A and 10B; and 12A and 12B. The new figures are properly labeled as “Replacement Sheet” in the top margin, pursuant to 37 C.F.R. 1.121(d). Applicants also submit marked-up copies of the drawings, showing the corrections made, labeled as “Annotated Sheets.” As shown in the Annotated Sheets, the amendments consist of labeling each panel shown in these Figures separately, and do not add new matter.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge the fees for extension of time, and any additional fees that may be required, or credit overpayment to Deposit Account No. 08-1641, referencing Attorney's Docket No. 39766-0125A.

Respectfully submitted,

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FIG. 6A

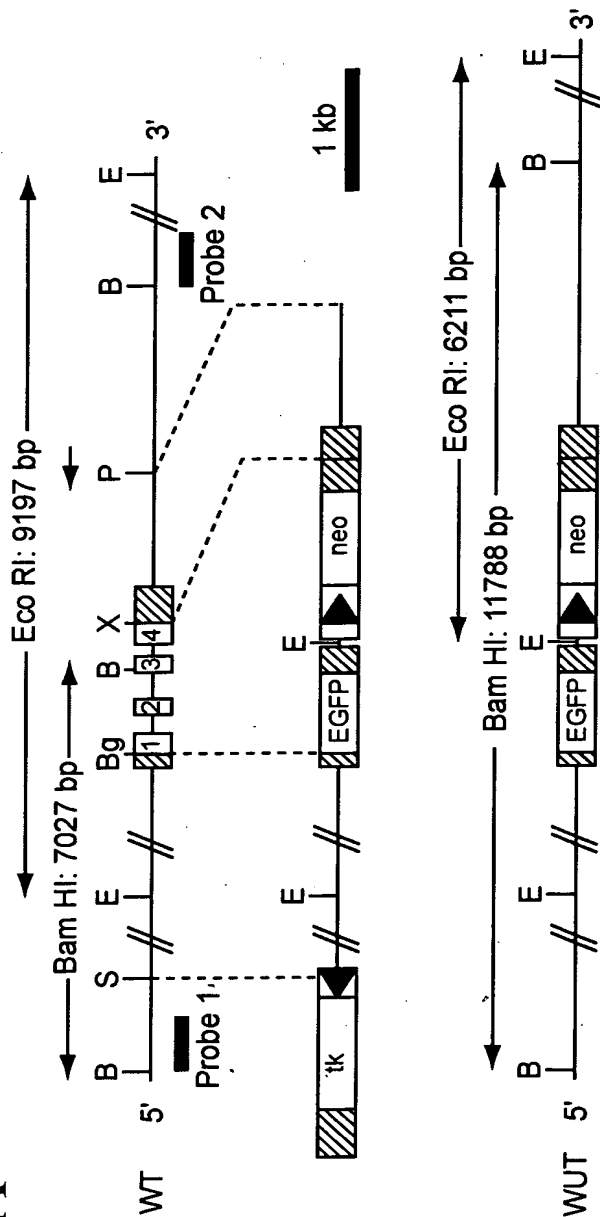


FIG. 6B

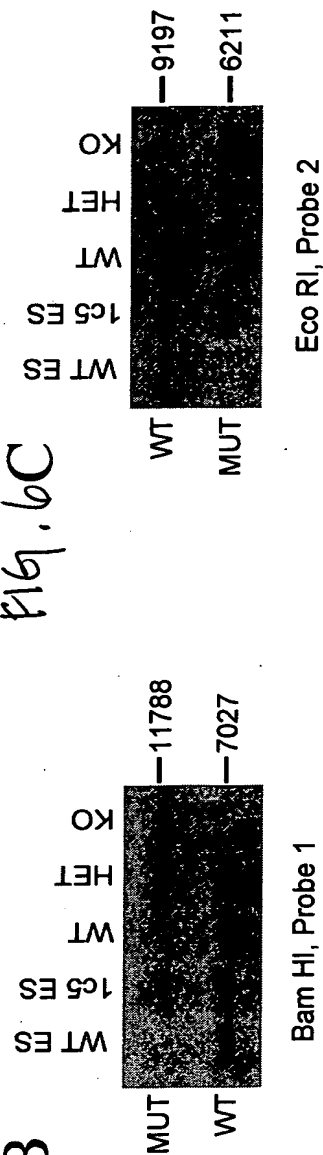
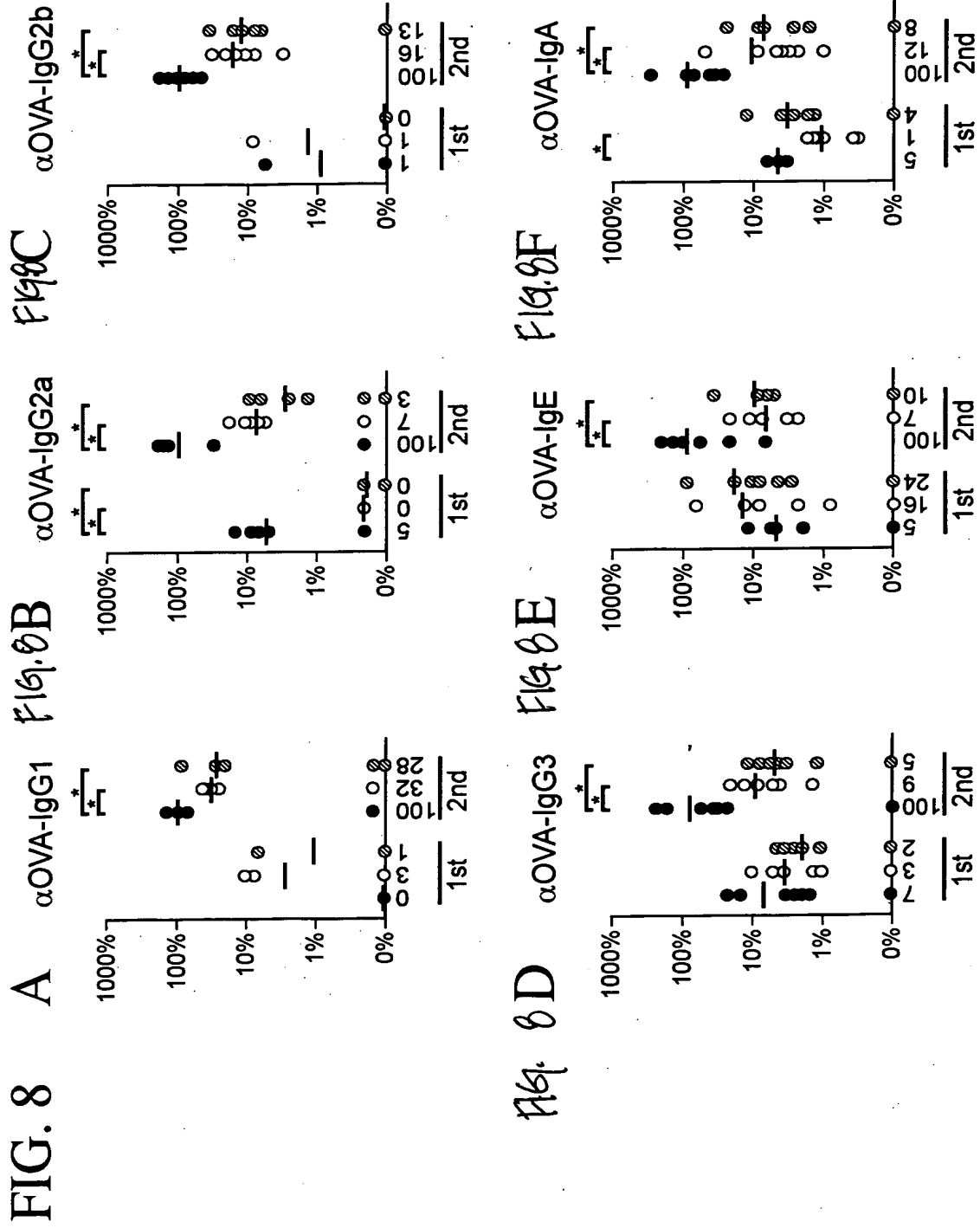


FIG. 6



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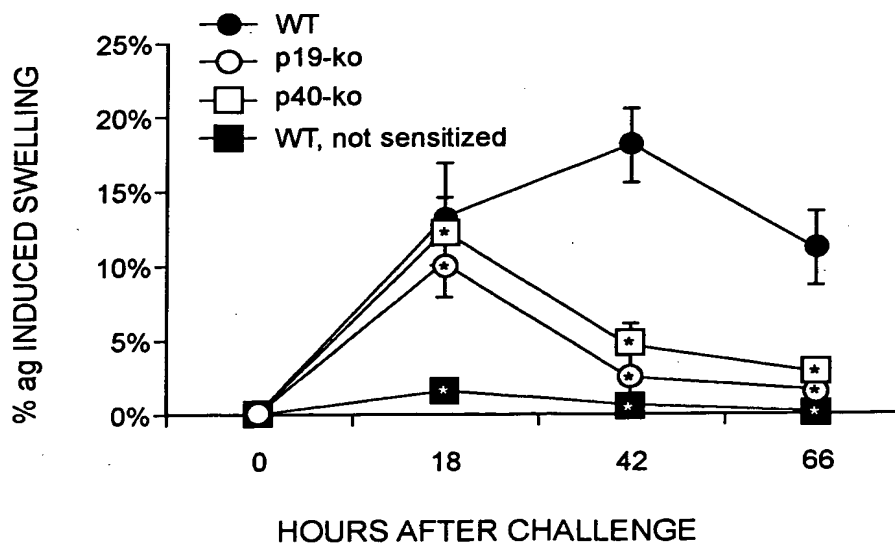
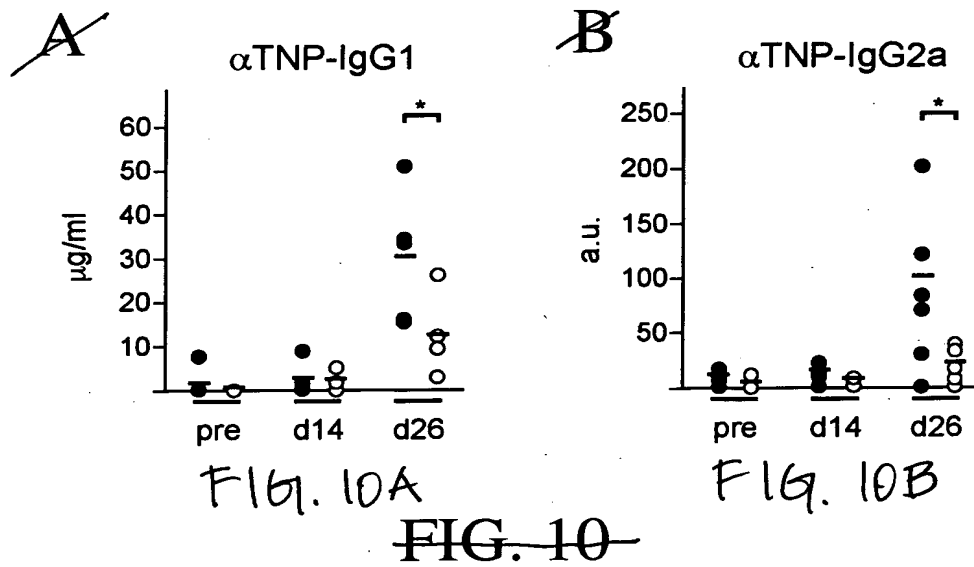


FIG. 11

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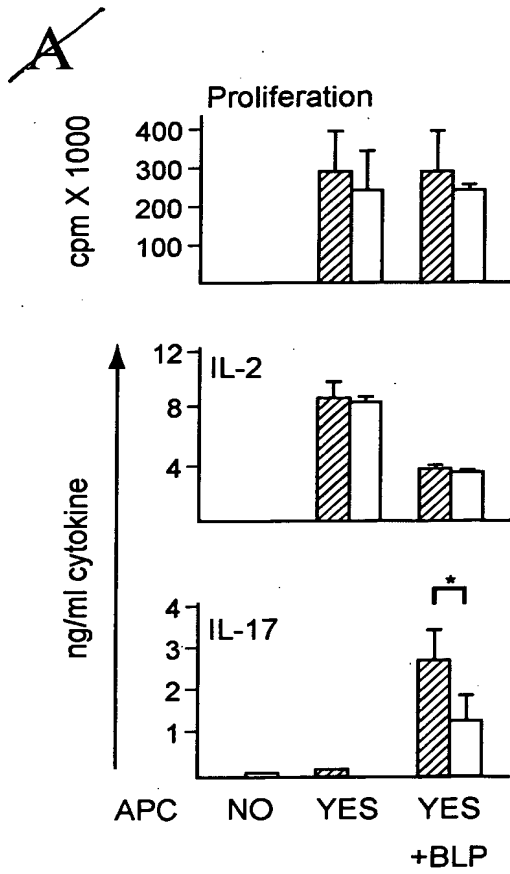


Fig. 12A

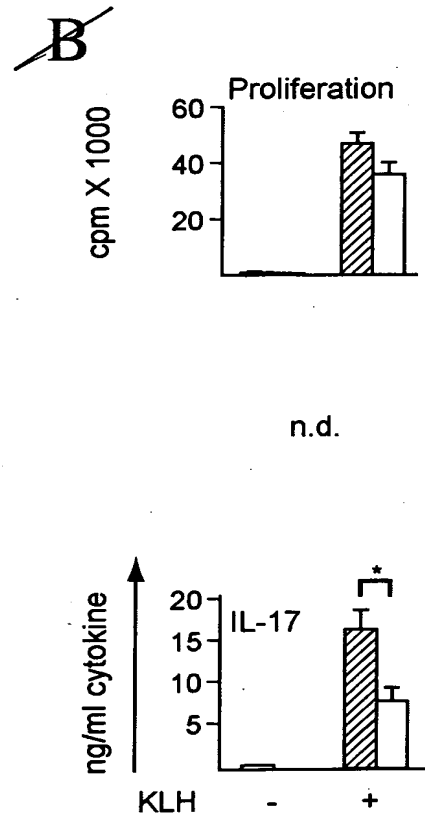


Fig. 12B

~~FIG. 12~~